Arthur Kornberg 1918–2007

Forty years ago, a Japanese press release issued on the occasion of a visit by Arthur Kornberg called him the "father of life in a test tube." This was in reference to his laboratory's 1967 feat of copying single-stranded circular DNA into a replicative form and then back to an infectious viral DNA strand using purified DNA polymerase and DNA ligase (Figure 1, left panel). Although a somewhat embarrassing mischaracterization of this stunning achievement, the comment offers a kernel of truth about Kornberg. He was in fact the father of DNA biochemistry, and his efforts gave rise to a revolution in our understanding of the mechanism of chromosome duplication. His laboratory, and more broadly his department at Stanford, provided the foundation for an emerging discipline of recombinant DNA and genetic engineering.

The life and accomplishments of this remarkable man are chronicled in his autobiography, *For the Love of Enzymes*, and in a shorter version published as a Perspective chapter in the *Annual Reviews of Biochemistry*, entitled *Never a Dull Enzyme* (58: 1–30, 1989). As a child of a Lower East Side New York City working class immigrant family, the precocious Kornberg entered the City College of New York at age 15 and decided to pursue a medical career. The prevailing anti-Semitism of the time limited his options and the only institution to which he was admitted, the University of Rochester, did so in spite of objections raised by the Dean of the Medical School (of course they now have a research building named in Arthur's honor). After an internship, Arthur enlisted in the Coast Guard in 1941 and was posted as a ship's physician, which ended rather abruptly in 1942 when, as Arthur once admitted, "the ship's Captain didn't seem to know who was in charge."

Arthur began his research career in a position at the National Institutes of Health (NIH) where he engaged in physiology studies in nutritional sciences. His initial work on vitamins led to an interest in enzymes that flourished in collaboration with Bernard Horecker at the NIH and in brief sojourns in Severo Ochoa's lab then at New York University and in Carl and Gerti Cori's lab at Washington University, St. Louis. Beginning with his experience in Ochoa's lab, and for the rest of his life, Arthur committed to the principle that any complex cellular process from nucleotide metabolism to chromosome replication can and must be examined with pure enzymes and substrates.

As a rising star, he caught the attention of Carl and Gerti Cori and, in 1953, Arthur was recruited to be chair of the microbiology department. He assembled a team of fellows and colleagues (including Bob Lehman, Dale Kaiser, Paul Berg, and Dave Hogness), who would become the nucleus of the future Biochemistry Department at Stanford University. During the Washington University years, Arthur embarked on stud-

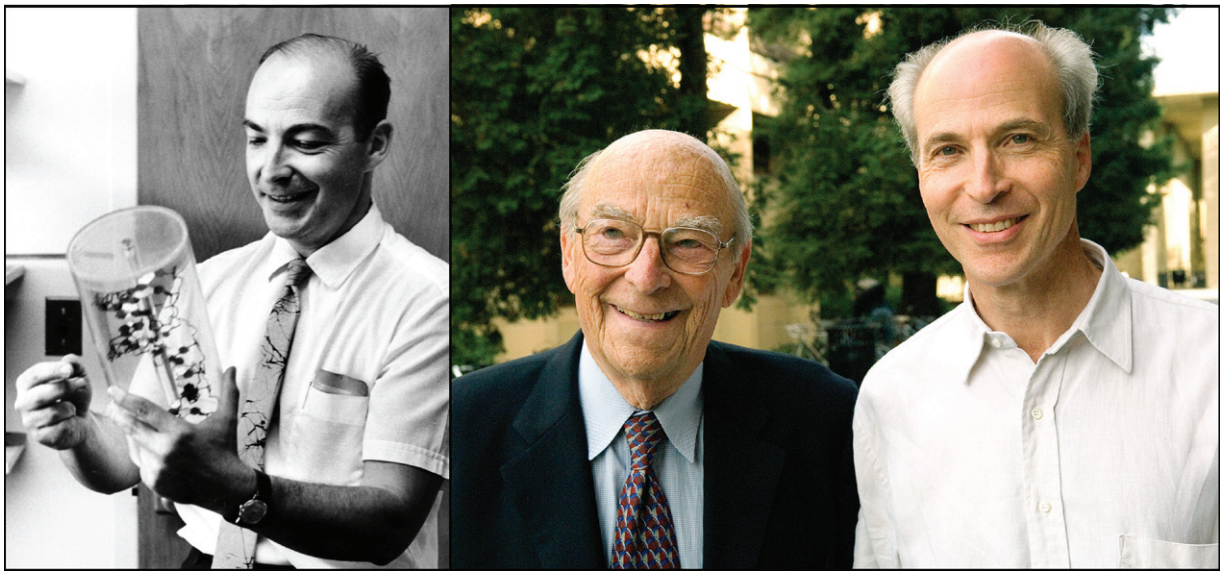

Figure 1. Arthur Kornberg, a Life in Enzymes
(Left panel) Kornberg shared the 1959 Nobel Prize in Physiology or Medicine with Severo Ochoa for their test-tube synthesis of nucleic acid, a discovery that led to recombinant DNA approaches and genetic engineering. (Right panel) Arthur Kornberg with his son, Roger, also at Stanford University, after Roger received the 2006 Nobel Prize for Chemistry. Photographs courtesy of Stanford University News Service (left)/Linda A. Cicero, Stanford University News Service (right).

ies that led to his discovery of DNA polymerase and his 1959 Nobel Prize in Physiology or Medicine. Having established pathways of enzymatic nucleotide biosynthesis, Arthur had available a precious resource of ^{14}C thymidine from his pharmacology colleague, Morris Freidkin, which he used to measure nucleotide incorporation into polymers dependent on addition of a crude extract of *Escherichia coli* and "primer" DNA. At first the signal was feeble, just a few counts above background. But the conviction that this represented authentic synthetic DNA encouraged Arthur, his technician Ernie Sims, and two postdoctoral fellows, Bob Lehman and Maurice Bessman, to optimize and ultimately to purify the first nucleic acid polymerase and to draw the revolutionary conclusion that the enzyme took its instructions from template DNA. Unfortunately, the work was not greeted with enthusiasm at the *Journal of Biological Chemistry* because the cantankerous Erwin Chargaff refused to accept that the product was authentic DNA.

In 1957, because of space restrictions at Washington University, Arthur negotiated a move to Stanford. When confronted with the news of this move to California, Carl Cori lamented "but where will you vacation if you move there?" Stanford Medical School was moving from San Francisco and Arthur was joined by his team from St. Louis and new faculty member Robert Baldwin, followed a few years later by Lubert Stryer and George Stark. This expanded group comprised the core of what would quickly become the preeminent Biochemistry Department in the country, particularly in reference to transactions involving nucleic acids.

Fresh from his triumph of a Nobel Prize at the tender age of 41, Arthur focused on the mysterious and multiple catalytic activities of DNA polymerase. He discovered that the enzyme had the capacity to degrade double-stranded DNA in the 5′-3′ direction, the same polarity as the synthetic reaction, and to degrade single-stranded DNA in the 3′-5′ direction. These nucleolytic activities proved crucial for correcting DNA errors. The 5′-3′ exonuclease repairs DNA damage by excision and resynthesis, and the 3′-5′ activity improves the fidelity of DNA replication by trimming recently added mismatched bases. Arthur and others, notably Hans Klenow, discovered that the enzyme was organized in independent domains, one containing the polymerase and the 5′-3′ exonuclease, and the other the 3′-5′ nuclease.

At the same time, phage T4 was found to encode its own DNA polymerase, essential for replication of phage DNA and containing similar nuclease activities. Genetic studies showed that the T4 polymerase 3′-5′ nuclease was required for high-fidelity DNA replication. New enzymes of DNA assembly, notably bacterial and phage DNA ligases, were discovered at Stanford in the Kornberg and Lehman labs, by Marty Gellert at the NIH, by Charles Richardson at Harvard, and by Jerry Hurwitz at Albert Einstein Medical School. Challenged to provide further support for a role of the bacterial polymerase in chromosome replication, Arthur's lab engineered the production of synthetic infectious ØX174 DNA. In two papers published in sequential issues of the *Proceedings of the National Academy of Sciences*, Arthur's lab presented the best evidence that these enzymes could engage in high-fidelity and complete chromosome replication.

At the same time, in many other laboratories around the world, the mechanism of DNA replication and repair was being pursued by more genetic and physiologic methods. A growing concern about the role of DNA polymerase in chromosome replication came from the very discoveries that made this such a fascinating enzyme. Its multiple activities in repair of DNA damage and its relatively slow rate of chain polymerization in relation to the rapid rate of chromosome fork movement suggested a role for the polymerase in DNA damage control. This view came to a head in the summer of 1969 with the discovery by John Cairns, then in transition from the position of Director of the Cold Spring Harbor Laboratory, of a mutation in the DNA polymerase gene of *E. coli*. Cairn's bacterial mutant displayed no polymerase activity in standard in vitro reactions yet showed nearly normal growth and chromosome replication in vivo but with clearly compromised DNA repair processes.

The clash of cultures, biochemistry and genetics, reinvigorated the field, although Arthur, who was in that era dismissive of the genetic approach, used the event to reconsider his premise and his focus on the one DNA polymerase.

At around this time, Friedrich Bonhoeffer in Germany developed a concentrated permeabilized *E. coli* cell lysate that showed promise for reproducing chromosome replication dependent on the DNA genes defined by the isolation of temperature-sensitive replication mutants. Arthur enlisted a team to investigate replication of the single-stranded circular templates, M13 and ØX174. His recent success in copying the ØX174 template depended on the use of a crude source of DNA primers, a boiled extract of *E. coli*, because the DNA polymerase could not initiate a chain de novo. Thus, Arthur sought a better defined source of primer and a cell-free extract that offered an ease of manipulation that was lacking in the Bonhoeffer system.

Several developments propelled the lab in a new direction. Arthur conceived of the notion that RNA polymerase, known to initiate synthesis of mRNA chains de novo, could serve to prime DNA chain growth. The notion that RNA may play a structural role in replication at the chromosome origin had been suggested but with no mechanistic connection to DNA chain initiation. A simple series of experiments using the M13 template documented the involvement of RNA polymerase in DNA strand initiation in vivo and in vitro. The ØX174 template proved more complex involving a new RNA primase, the dnaG protein, and a host of other replication proteins that the cell uses for growth at the chromosome replication fork.

Quite independently, and by an amazing coincidence, Tom Kornberg, Arthur's second son, working in the laboratory of Malcolm Gefter, then

at Columbia University, discovered the DNA polymerase responsible for *E. coli* chromosome replication, encoded by the bacterial *dnaE* gene. This enzyme, which was then purified in Arthur's lab, is a large hetero-oligomeric complex that organizes growth of the leading and lagging strands at the chromosome replication fork. Following that and for the next 20 years, Arthur's lab and many of his successful students and fellows completed the purification and characterization of all *E. coli* replication proteins, a truly monumental achievement.

In 1991, Arthur began a new phase of his career returning to an old love he and his wife Sylvy shared: enzymatic synthesis of polyphosphate. As with everything that Arthur touched, this became his passion and the most important subject that one could possibly study!

Much has been made of the Kornberg style of hard work and focus on basic principles. He expected his coworkers to match his absolute devotion to the research. And although he was a great mentor, it was more in the form of role model than teacher. His research group was never larger than a dozen, and yet students and fellows who may not have excelled before or after their years in Arthur's lab performed at their peak potential while they were in his lab. Arthur decried the emphasis on applied and "translational" medical research. He remained a powerful voice for the primacy of basic research.

Arthur and Jim Watson represented the opposite extremes of nucleic acid research. Although Arthur's work in DNA polymerase began in the wake of the discovery of the structure of DNA, he insisted that this did not inform his studies on the enzymatic process, at least not initially. When Watson published the *Double Helix*, Arthur, quite aside from those who considered the book scandalous, felt Watson gave young scholars the wrong impression that all you needed was one good idea to make a career. Of course, conceiving of the structure of DNA was an exceptionally good idea, but Arthur had unpredictable insights that motivated much of his hard work. Examples include his discovery that DNA polymerase progresses in the 5′-3′ direction, which he used to measure dinucleotide frequencies and which provided the first experimental evidence of the antiparallel nature of duplex DNA; his quest to synthesize a biologically active chromosome; his conception that RNA polymerase could prime DNA chain growth; and most importantly, his unwavering faith in the power of enzymatic reconstitution of complex cellular processes. Together these remarkable insights constitute a legacy of brilliance matched by his technical achievements.

Although Arthur is defined by his science, his family came first: his dear wife of 43 years, Sylvy, with whom he shared the years of his rise to prominence and a laboratory at the NIH and Washington University, his second wife Charlene, a scientific illustrator who did much of the art work on Arthur's books and publications, and finally Carolyn, his companion and wife for the last nine years of his life.

Nothing could compare to the love and devotion Arthur felt for his sons, Roger, Tom, and Ken, and their young families, each tremendously accomplished in his own right and each with a connection to biology. Tom went on to a career in developmental biology at UCSF. Ken is an architect specializing in the design of science laboratories. And Roger, whose structural elucidation of the mechanism of transcription led to his 2006 Nobel Prize in Chemistry, provided Arthur with the proudest moment of his life (Figure 1, right panel).

On a personal note, in the deaths of Arthur and my great Berkeley colleague Dan Koshland, I have lost my two most influential mentors. Arthur tolerated me (barely) as an insecure and arrogant rookie graduate student. He taught me rigor and discipline and showed by example the power of biochemistry. I regret not telling him this, but I am not ashamed to say that I have spent the last 30+ years of my career trying to live up to his standard. Luminaries of this stature are rare but Arthur and Dan are irreplaceable. John Updike captured this in his poem *Perfection Wasted*, which ends, "The memories packed in rapid-access file. The whole act. Who will do it again? That's it: no one; imitators and descendents aren't the same."

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